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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 4336
Serial No.:10/028,988	Art Unit: 3763
Filed: December 28, 2001	Examiner: Manuel A. Mendez
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-022-999 (500752-999021; P-4901P5)

SUPPLEMENTAL DECLARATION OF DR. RONALD J. PETTIS UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as the '988 application).

2. I am currently a Senior Scientist, at Becton, Dickinson and Company, Inc. which is the assignee of the '988 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have been asked to comment on whether intradermal delivery as practiced in accordance with the methods of the invention would always necessarily result in a higher AUC, C_{max} and/or a shorter T_{max} as compared to subcutaneous delivery.

5. As already described in the Declaration I submitted in connection with U.S. Application Serial No. 09/606,909 on January 6, 2005 ("the January Declaration"), my co-inventors and I developed an intradermal (ID) drug delivery system that results in an

improved pharmacokinetic profile similar to that observed with subcutaneous (SC) delivery, but with enhanced pharmacokinetic parameters. The improved pharmacokinetic profile can be manifested in two or more of the traditionally measured parameters, *e.g.*, faster T_{max} (the time required for the drug to reach a maximum serum concentration), increased C_{max} (the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration), or increased AUC (the area under the serum concentration curve, which is a measure of bioavailability).

6. However, the injection of a drug to the intradermal comapartment does not inevitably result in an increased AUC, an increased C_{max} and/or a faster T_{max}. Various factors affect the resultant pharmacokinetic parameters, including the particular substance delivered, the rate of delivery used, and the mode of delivery. When a substance is delivered at a varied rate, pressure, volume or depth, a different pharmacokinetic profile may be obtained as evidenced by the data presented below. In particular, when Almotriptan was administered to the ID compartment as described in ¶¶ 7-9 below, the result was a pharmacokinetic profile nearly identical to SC delivery.

7. In the '988 application, Axert®, Almotriptan malate ("Almotriptan"), was delivered in a Yucatan mini pig model using a microneedle device (see Example XII of the '988 application). The microneedle had a total exposed length of 1 mm, designed such that the penetration of the needle outlet was limited to 1 mm. The Almotriptan delivery was controlled using a syringe pump (Harvard PHD 2000, Harvard Apparatus, Holliston, MA) wherein the rate of delivery was 45 μL/min and 180 μL/min. The delivery duration was 2-2.5 minutes. The pharmacokinetic parameters of intradermal and subcutaneous delivery of Almotriptan are summarized in Table 3 of the '988 application and reproduced below, in part, for convenience.

PK parameters	SC	ID
C_{max}(ng/mL)	61±19.4	63.6 (26.1)
T_{max}(h)	0.13 (0.05)	0.14 (0.008)
AUC	55.9 (6.04)	53.3 (15.7)

Table 3: Almotriptan PK Parameters Following SC and ID Administration

8. It is clear from an inspection of Table 3 that the pharmacokinetic profile and pharmacokinetic parameters of Almotriptan delivered to the intradermal space are similar to SC delivery, but not necessarily enhanced. Indeed, the AUC, C_{max} and T_{max} resulting from intradermal delivery as set out above closely resemble those resulting from SC delivery. This example thus unequivocally demonstrates that injection of a drug to the ID compartment does not inevitably result in enhanced pharmacokinetic parameters as compared to subcutaneous delivery.

9. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: August 9, 2006

/Ronald J. Pettis/

RONALD J. PETTIS